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# Combinatorial Chemistry Online

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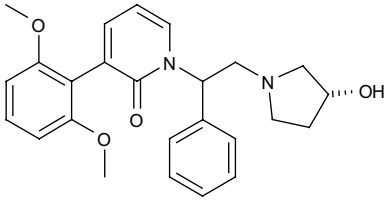
## 1. Current literature highlights

### 1.1. Kappa opioid receptor agonists

Non-peptide ligands of the kappa opioid receptor (KOR) have been known for many years. These KOR agonists were initially targeted towards various pain indications but preliminary clinical studies showed that they produced severe centrally-mediated side effects such as diuresis, sedation and dysphoria. As a result KOR agonists were dropped from development and no selective KOR agonist compound has yet reached the market. A strategy has been described for the preparation of KOR agonists with the introduction of more polar substituents on the core template to increase polar surface area and reduce lipophilicity, thereby reducing the compounds' ability to cross the blood-brain barrier. Such compounds may still act at peripheral KORs and may be useful for the treatment of visceral pain, whilst avoiding the well-documented side effects of previous KOR agonists.[1]

Several libraries have been prepared, both in solution phase and on Wang resin solid phase. Purified compounds from these libraries were isolated and screened against opioid receptors using classical filter binding assays, measuring the displacement of the appropriate radiolabelled ligand from membranes of HEK293 cells over-expressing the requisite human opioid receptor. One of the most potent compound isolated was (i) which possessed a kappa opioid binding $IC_{50}$ of 9.8 nM, with >1000-fold selectivity over the δ-opioid and >390-fold selectivity over the μ-opioid receptor.




(i)

### 1.2. Neuraminidase inhibitors from dynamic combinatorial libraries

Dynamic combinatorial chemistry (DCC) is a new approach to the integration of combinatorial chemistry and screening based on the shift of chemical equilibrium in a mixture of interconverting components driven by a molecular target. This process results in the preferred formation of one or a few mixture components that form the strongest noncovalent complexes to the target. The successful application of DCC to the discovery of new ligands for biological targets relies on the synergy of several factors: use of reversible reactions compatible with aqueous media, availability of functionally diverse library building blocks, and robust methods of mixture analysis. The first use of ketones as building blocks of dynamic libraries has been reported.[2]

The structures of library components selected and amplified by the target, reveal building block combinations that can be used to generate highly active inhibitors with properties at least matching those of commercial drugs. Neuraminidase, a key enzyme involved in influenza virus propagation, has been used to exemplify the approach of DCC. Diamine (ii) which is structurally similar to some known neuraminidase inhibitors was used as the scaffold for the dynamic libraries.[3] Equilibration of the scaffold with a mixture of 22 ketones was expected to produce a set of imines, the distribution of

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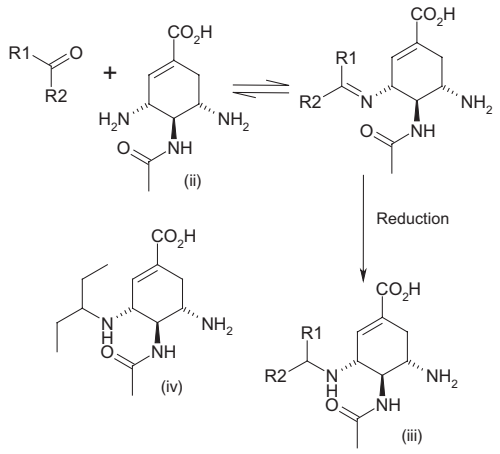
which would be altered by the addition of neuraminidase. The imines were then reduced to the secondary amines of general structure (iii), the composition of which was analysed by LC/MS. Addition of the enzyme target resulted in a dramatic amplification of selected amine peaks. It was demonstrated that the binding properties (as measured by $K_i$ values) of the amines (iii) correlate well with their amplification in the DCC experiment. One of the most potent compounds synthesised with a $K_i$ of 85 nM was (iv). This work has provided neuraminidase inhibitors from a DCC approach that are even more potent than the native forms.




## 2. A summary of the papers in this month's issue

### 2.1. Solid-phase synthesis

The synthesis of 1,4,8-triazaspiro[4.5]decan-2-one derivatives from *N*-benzyl-4-piperidone and *N*-protected amino acid amides on SynPhase™ Lantern solid support has been reported.[4]

A method for synthesizing combinatorial libraries of unsymmetrically substituted tetra-*meso*-phenyl porphyrins on polystyrene based resin has been described.[5]

Five-dimensional libraries of dipeptide amides have been readily prepared using a solid-phase tandem Petasis–Ugi multi-component condensation protocol on either a RINK amine or Universal RINK isonitrile resin.[6]

The on-resin reduction of head-to-tail cyclotetrapeptides, anchored to a solid support by the side-chain of a trifunctional amino acid, has been shown to be an efficient synthetic strategy.[7]

The generation of macro-heterocycles starting from resin-bound orthogonally protected lysine and using nucleophilic aromatic substitution has been reported, and used for the synthesis of libraries in an attempt to establish lead drug candidates.[8]

Efficient solid-phase synthesis of diverse 1,2,3-benzotriazin-4-ones using *tert*-butyl nitrite has been reported.[9]

An on-resin Ugi four-component reaction followed by an intramolecular nucleophilic aromatic substitution ($S_NAr$) has been developed for the rapid access to biaryl-ether containing macrocycles.[10]

Stille, Negishi, Suzuki and Sonogashira cross-couplings have been performed on solid-phase leading to aryl and alkynyl pyridylpiperazines in acceptable to good yields.[11]

A new method for the solid phase synthesis of benzothiazoles and 2-arylamino-3-carboxyl-4-hydroxy-5-arylthiophenes in high yields and purities has been described.[12]

The preparation of organic conjugates of oligonucleotides and peptides, peptide conjugates of oligonucleotides, and glycoconjugates of peptides on solid support has been reviewed.[13]

A method for the solid-phase synthesis of quinazoline-2,4-diones with various electron-withdrawing substituents on the aromatic ring has been described.[14]

### 2.2. Solution-phase synthesis

Parallel synthesis of β-carbolines on soluble polyethylene glycol (PEG-OH) support has been demonstrated. One-pot condensation of polymer-bound tryptophan residues with various aldehydes and ketones has been carried out in the presence of *p*-TSA as a catalyst to deliver immobilized 1,2,3,4-tetrahydro-β-carbolines.[15]

A new, high yield multicomponent reaction providing multifunctionalized pyrido[2,3-*d*]pyrimidines in a microwave-assisted one-pot cyclocondensation of α, β-unsaturated esters, amidine systems and malononitrile (or ethyl cyanoacetate) has been described.[16]

Progress in the development of fluorous technologies for solution-phase parallel and mixture synthesis have been described in a recent review.[17]

A five-step solution-phase library synthesis, using a combination of polymeric reagents and polymer-assisted solution-phase purification protocols, of an α-ketothiazole library has been described. A variety of L-amino acid inputs were used to probe the S2 pocket of the tissue factor (TF) VIIa enzyme to influence both potency and selectivity.[18]

### 2.3. Library intermediates

A recent report describes methods for the preparation of the indole moiety or modification of the indole core on a variety of polymer-supported resins.[19]

The regiospecific syntheses of six monosaccharide scaffolds, containing a carboxylic acid, an azido and a free hydroxyl group were accomplished through the utilization of a key synthetic intermediate and used in generating combinatorial libraries using solid-phase methodologies.[20]

### 2.4. Novel resins and linkers

Trimellitic Anhydride Linker (TAL) has been introduced as an anchor in solid-phase synthesis allowing for immobilization of primary amines. The linker is stable under a broad range of reaction conditions including strong acid, base, and oxidants.[21]

Reverse-phase glass beads have been employed in Suzuki reactions to provide, in aqueous media, a route to diverse polar substrates in good yield and with low levels of palladium leaching.[22]

A new linker based on a chroman system is described for the side-chain anchoring of arginine and other guanidine-containing molecules.[23]

A novel linker possessing selenocyanate and a masked carboxylic acid was developed for the solid-phase synthesis of dehydropeptides. This linker was used to demonstrate the synthesis of the model compound of RGD-conjugated dehydropeptide.[24]

### 2.5. Solid-supported reagents

A novel polymer-supported triacetoxyborohydride reagent for reductive amination of aldehydes and ketones has been described. The bound reagent was found to be shelf-stable and provided broad scope and reactivity in reductive amination reactions under mild reaction conditions.[25]

A robust 'catch and release' synthesis of fused 2-alkylthio-3-substituted-pyrimidinones mediated by the polymer-bound base P-BEMP has been developed and used for the solution-phase synthesis of a representative 48-member combinatorial library.[26]

### 2.6. Library applications

A rapid structure–activity study was performed by parallel liquid synthesis on *N*,*N*′-disubstitution of 3-amino azepin-2-one to afford potent and specific farnesyl transferase inhibitors with low nM enzymatic and cellular activities.[27]

The parallel synthesis of novel inhibitors of procollagen C-terminal proteinase has been described.[28]

A new generation of indole-based peptide mimetics bearing a basic amine at the C-terminus, was developed by multistep, trityl resin-based approaches and found to be excellent PAR-1 antagonists.[29]

A library, evaluating a range of piperazines, piperidines and acyclic amines as replacements for the 4-hydroxy-4-phenylpiperidine moiety in a lead NK2 antagonist have been prepared.[30]

The synthesis of a library of compounds was undertaken to permit screening for synthetic agonists and antagonists of a *Pseudomonas aeruginosa* autoinducer.[31]

Structure-based drug design coupled with polymer-assisted solution-phase library synthesis has been utilized to develop a series of sub-nanomolar pyrazinone inhibitors of the tissue factor/Factor VIIa complex.[32]

An interdisciplinary research approach integrating chemistry and biology is illustrated by the synthesis and biological evaluation of lipidated peptides and proteins, and the delineation of a concept arguing for natural product-guided combinatorial chemistry.[33]

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